Resolution of racemic 2-isobornyl-4-methylphenol into enantiomers*

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Resolution of racemic 2-isobornyl-4-methylphenol into enantiomers was performed following its transformation into diastereomers by the reaction with (1*S*)-camphanoyl chloride.

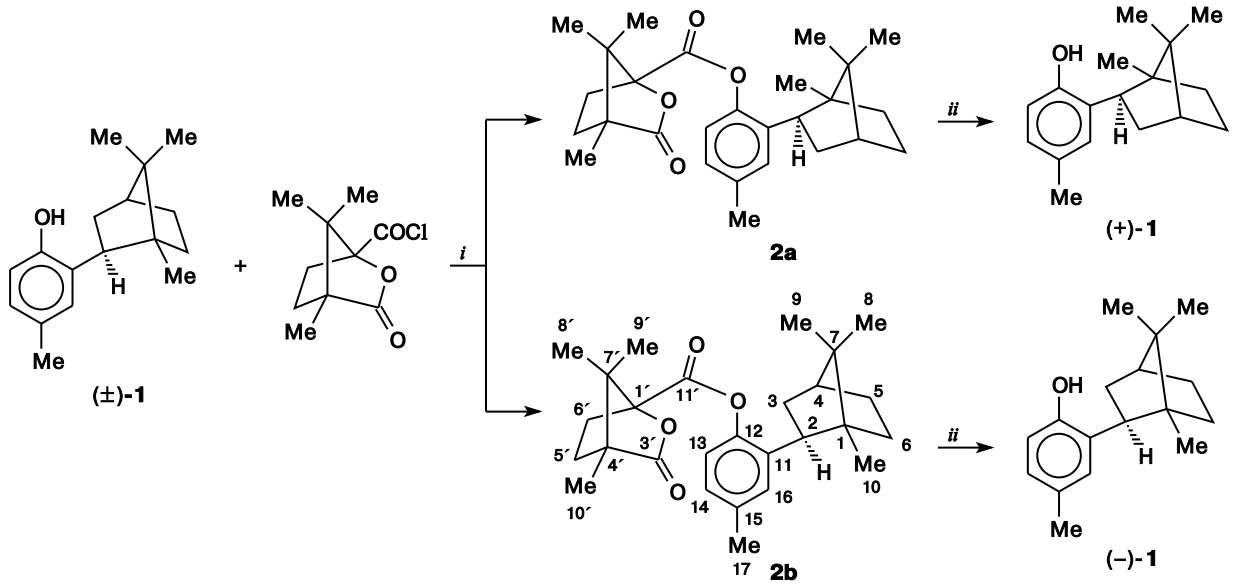
Key words: terpenophenols, 2-isobornyl-4-methylphenol, (1*S*)-camphanoyl chloride, diastereomers, enantiomers.

The phenols bearing isobornyl substituents exhibit antithrombogenic and antithrombocytic activities[1] and are used for the local treatment of infections and inflammation of the throat.[2] In some cases, the biological activities of enantiomers differ considerably;[3] therefore, with the aim of discovering new properties of terpenophenols and their derivatives, the preparation of their individual enantiomers becomes topical.

Earlier, we have reported the resolution of enantiomers of salicylic aldehydes bearing the isobornyl substituent in position 3 *via* diastereomeric imines.[4] Resolution of 2-isobornyl-4-methylphenol (±)-**1** using preparative chromatography on a chiral column was also described.[5] In the present work, we performed the resolution of compound (±)-**1** using a chiral reagent to obtain enantiomerically enriched terpenophenol **1** with one vacant *ortho*-position, which is interesting for further functionalization.

The acylation of the phenolic hydroxyl group with (1*S*)-camphanoyl chloride gave a mixture of diastereomeric esters **2a** and **2b** in the ratio 1 : 1 (Scheme 1). The resolution of **2a** and **2b** was carried out by column chromatography. The subsequent hydrolysis of the ester groups in these compounds resulted in enantiomerically enriched terpenophenols (+)-**1** and (−)-**1**. The diastereomeric pu-

Scheme 1



Reagents and conditions: *i*. Et_3N, DMAP, PhMe, 110 °C; *ii*. aq. KOH/THF, 20 °C.

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rity of derivatives **2a** and **2b** was established using ^{1}H NMR; the enantiomeric purity of compounds (+)-**1** and (−)-**1** was established by HPLC.

The identification of compounds (+)-**1** and (−)-**1** was performed on the base of the signs of their optical rotations with those reported in literature.[5] The absolute configuration of the chiral centers of compounds **2a** and **2b** was determined taking into account the absolute configuration of the enantiomers of compound **1** obtained by hydrolysis.

Experimental

The reactions were monitored by TLC on Sorbfil plates; the components were visualized by treatment of the plates with a solution of Bromocresol Purple. The ^{1}H and ^{13}C NMR spectra of the prepared compounds were recorded on a Bruker Avance II 300 spectrometer (300.17 and 75.5 MHz) in $CDCl_3$. The assignment of signals in ^{13}C NMR spectra was carried out using the DEPT method. The IR spectra were recorded on a Shimadzu IR Prestige 21 IR-Fourier-spectrometer in KBr pellets. The optical rotations were measured on a Kruss Optronic P3002RS polarimeter. The HPLC analysis of compound (±)-**1** and enantiomers (+)-**1** and (−)-**1** was carried out using a Daicel Chiralcel OD-H column. Silica gel (Alfa Aesar, 0.06—0.2 mm) was used for column chromatography. Compound (±)-**1** was prepared by the known method.[6] (1*S*)-Camphanoyl chloride, Et_3N, and DMAP (Alfa Aesar, Sigma—Aldrich) were used for the acylation.

Synthesis and resolution of esters. A mixture of phenol (±)-**1** (1.0 g, 4.1 mmol), (1*S*)-camphanoyl chloride (0.98 g, 4.5 mmol), Et_3N (0.63 mL, 4.5 mmol), and DMAP (0.05 g, 0.41 mmol) in 50 mL of dry toluene was refluxed for 5 h with stirring under argon. The reaction mixture was cooled to room temperature, $Et_3N \cdot HCl$ was filtered off. The residue was concentrated and separated by column chromatography (eluent, PhH). The yield of compound **2a** was 0.71 g (41%), the yield of compound **2b** was 0.75 g (43%) with diastereomeric purity >99 and >93%, respectively.

4-Methyl-2-(*exo*-(1*R*,2*S*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]-hept-2-yl)phenyl (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo-[2.2.1]heptane-1-carboxylate (2a). Colorless powder, m.p. 144—146 °C, R_f 0.38 (PhH), $[\alpha]_D^{22}$ +4.9 (*c* 0.22, CH_2Cl_2). Found (%): C, 76.48; H, 8.48. $C_{27}H_{36}O_4$. Calculated (%): C, 76.38; H, 8.55. IR (KBr), ν/cm^{-1}: 1790, 1767 (C=O), 1259 (C—O). ^{1}H NMR ($CDCl_3$), δ: 0.80 (s, 3 H, C(10)H_3); 0.84 (s, 3 H, C(9)H_3); 0.90 (s, 3 H, C(8)H_3); 1.14 (s, 6 H, C(8′)H_3, C(9′)H_3); 1.17 (s, 3 H, C(10′)H_3); 1.24—1.44 (m, 2 H, H(3), H(4)); 1.57—1.68 (m, 2 H, H(5)); 1.71—1.86 (m, 3 H, 2 H(6) + H(5′)); 1.94—2.03 (m, 1 H, H(5′)); 2.12—2.22 (m, 2 H, H(3), H(6′)); 2.34 (s, 3 H, C(17)H_3); 2.52—2.61 (m, 1 H, H(6′)); 2.88 (t, 1 H, H(2), *J* = 8.8 Hz); 6.87—6.90 (m, 1 H); 6.98—7.01 (m, 1 H); 7.25 (br. d, 1 H) (H(13), H(14), H(16)). ^{13}C NMR ($CDCl_3$), δ: 9.72 (C(10′)); 12.64 (C(10)); 16.75, 16.94 (C(8′), C(9′)); 20.54 (C(9)); 21.33 (C(17)); 21.39 (C(8)); 27.35 (C(5)); 28.89, 31.02 (C(5′), C(6′)); 34.26 (C(3)); 40.11 (C(6)); 45.50 (C(2)); 46.08 (C(4)); 47.97 (C(7)); 50.07 (C(1)); 54.60, 54.88 (C(4′), C(7′)); 90.70 (C(1′)); 121.31, 126.94, 129.54 (C(13), C(14), C(16)); 134.95, 135.34, 147.47 (C(11), C(12), C(15)); 166.48, 178.04 (C(3′), C(11′)).

4-Methyl-2-(*exo*-(1*S*,2*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]-hept-2-yl)phenyl (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo-[2.2.1]heptane-1-carboxylate (2b). Colorless powder, m.p. 118—121 °C, R_f 0.26 (PhH), $[\alpha]_D^{22}$ +4.0 (*c* 0.93, CH_2Cl_2). Found (%): C, 76.52; H, 8.52. $C_{27}H_{36}O_4$. Calculated (%): C, 76.38; H, 8.55. IR (KBr), ν/cm^{-1}: 1792, 1763 (C=O), 1261 (C—O). ^{1}H NMR ($CDCl_3$), δ: 0.75 (s, 3 H, C(10)H_3); 0.84 (s, 3 H, C(9)H_3); 0.90 (s, 3 H, C(8)H_3); 1.11 and 1.21 (both s, by 3 H, C(8′)H_3, C(9′)H_3); 1.19 (s, 3 H, C(10′)H_3); 1.23—1.45 (m, 2 H, H(3), H(4)); 1.58—1.67 (m, 2 H, H(5)); 1.75—1.87 (m, 3 H, 2 H(6) + H(5′)); 1.97—2.05 (m, 1 H, H(5′)); 2.14—2.28 (m, 2 H, H(3), H(6′)); 2.34 (s, 3 H, C(17)H_3); 2.55—2.65 (m, 1 H, H(6′)); 2.93 (t, 1 H, H(2), *J* = 8.8 Hz); 6.87—6.90 (m, 1 H); 6.99—7.01 (m, 1 H); 7.26 (br. d, 1 H) (H(13), H(14), H(16)). ^{13}C NMR ($CDCl_3$), δ: 9.69 (C(10′)); 12.76 (C(10)); 16.95, 17.02 (C(8′), C(9′)); 20.47 (C(9)); 21.33 (C(17)); 21.46 (C(8)); 27.32 (C(5)); 29.09, 31.08 (C(5′), C(6′)); 34.21 (C(3)); 39.87 (C(6)); 45.48 (C(2)); 45.79 (C(4)); 48.00 (C(7)); 49.99 (C(1)); 54.49, 54.84 (C(4′), C(7′)); 90.79 (C(1′)); 121.37, 126.96, 129.65 (C(13), C(14), C(16)); 134.88, 135.40, 147.38 (C(11), C(12), C(15)); 166.24, 177.81 (C(3′), C(11′)).

Hydrolysis of the ester group in compounds 2. Ester **2a** or **2b** (0.5 g, 1.2 mmol) was dissolved in 10 mL of THF, 5 mL of 5 *M* aqueous KOH was added, and the mixture was stirred for 15 h at room temperature. After the reaction was complete, the organic layer was separated, washed with brine (2×10 mL), and dried with anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by column chromatography (eluent, *n*-hexane—Et_2O, 35 : 1).

(1*R*,2*S*,4*S*)-1,7,7-Trimethyl-2-(2-hydroxy-5-methylphenyl)-bicyclo[2.2.1]heptane ((+)-1). Colorless oil. Yield 0.27 g (94%), enantiomeric purity >99.5%, $[\alpha]_D^{22}$ +59.6 (*c* 0.56, $CHCl_3$), see Ref. 5: $[\alpha]_D^{20}$ +60.5 (*c* 0.62, $CHCl_3$).

(1*S*,2*R*,4*R*)-1,7,7-Trimethyl-2-(2-hydroxy-5-methylphenyl)-bicyclo[2.2.1]heptane ((−)-1). Colorless oil. Yield 0.28 g (96%), enantiomeric purity 93.6%, $[\alpha]_D^{22}$ −54.8 (*c* 0.61, $CHCl_3$), see Ref. 5: $[\alpha]_D^{20}$ −59.9 (*c* 0.45, $CHCl_3$).

The spectral characteristics of compounds (+)-**1** and (−)-**1** agree with data described in literature for the racemate of this compound.[5]

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